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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the application of

Tadashi MUKAI et al — Group Art Unit: 1615

Serial No.: 10/089,442 — Examiner: Humera N. Sheikh

Filed: March 29, 2002

For: Coated Preparation Soluble In The Lower Digestive Tract

DECLARATION

Honorable Commissioner of
Patents and Trademarks
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Tadashi MUKAI, a citizen of Japan, declare as follows.

1. I was graduated from The University of Tokushima, Faculty and School of Engineering, Chemical Engineering in 1983.

2. Since 1983 up till the present, I have been in the employ of Otsuka Pharmaceutical Co., Ltd., and since 1989, I have been engaged in research and development works at Formulation Research Institute of this company.

3. I am one of the inventors of the present U.S. Patent Application No. 10/089,442 and am familiar with the subject matter thereof, and I have read the cited Maruyama et al., EP 0 648 487 and Eichel et al., EP 0 391 518 and am familiar with the subject matter thereof.

4. Under my direction, the following comparative experiment has been done.

Experiment: Dissolution rate of medicament in coated granules

Coated granules to be tested:

(1) Preparation of core granule for coating:

In accordance with the formula as shown in Table I, the core granules were prepared in the same manner as described in the description of the present U.S. Application No. 10/089,442, Example 10.

Table I

Components of the core granules	Example 10 in U.S. Appln. No. 10/089,442
Cilostazol	150 mg
Hydroxypropylmethylcellulose acetate succinate	60 mg
Hydroxypropylmethylcellulose	15 mg
Sodium laurylsulfate	12.5 mg
Sodium chloride	-
Sodium citrate	7.5 mg
Citric acid	7.5 mg
Polysorbate 80	7.5 mg
Totally	260 mg

(2) Preparation of coated granules:

The core granules prepared above were coated with the coating dispersion having the components as shown in the following Table II in the same manner as described in the description of the present U.S. Application No. 10/089,442 to give the coated granules.

Table II

Components for coating dispersion	Product of the present invention	Comp. Ex. A	Comp. Ex. B
HPMCAS*1)	7.0% (80.0 mg)	7.0% (80.0 mg)	7.0% (80.0 mg)
Triethyl citrate	3.2% (32.0 mg)	3.2% (32.0 mg)	3.2% (32.0 mg)
Talc	3.5% (40.0 mg)	3.5% (40.0 mg)	3.5% (40.0 mg)
sodium laurylsulfate	0.21% (2.4 mg)	0.21% (2.4 mg)	0.21% (2.4 mg)
Citric acid	0.21% (2.4 mg)*2)	-	3.5% (40.0 mg)*3)
Purified water	Remainder	Remainder	Remainder

*1) HPMCAS: Abbreviation of hydroxypropyl methylcellulose acetate succinate

*2) Citric acid was contained in 3 parts by weight to 100 parts by weight of HPMCAS.

*3) Citric acid was contained in 50 parts by weight to 100 parts by weight of HPMCAS.

Test of dissolution rate

A 0.3 % aqueous solution of sodium laurylsulfate (720 ml) which was adjusted to pH 6.5 by a citrate buffer was used as a dissolution solvent. The coated granules obtained above (the product of the present invention and in Comparative Examples A and B) were subjected to the dissolution test at 50 rpm by Paddle method as defined in Japanese Pharmacopeia. By using 0.3% aqueous solution of sodium laurylsulfate which was adjusted to pH 1.2 and that which pH was not controlled (initial pH 5.2) as the dissolution solvent, the product of Comparative Example B was tested likewise. The dissolution profile of the coated granules thus tested are shown in the accompanying Fig. 1. Further, the time of dissolution of 5% of medicament as a lag time is also shown in the following Table III.

Table III

	Dissolution solvent	5% dissolution time
The product of the present invention	0.3 % aqueous sodium laurylsulfate solution (pH6.5)	312 minutes
Product of Comp. Ex. A	0.3 % aqueous sodium laurylsulfate solution (pH6.5)	65 minutes
Product of Comp. Ex. B	0.3 % aqueous sodium laurylsulfate solution (pH6.5)	64 minutes
	0.3 % aqueous sodium laurylsulfate solution (pH1.2)	60 minutes
	0.3 % aqueous sodium laurylsulfate solution (not control of pH, initial pH 5.2)	64 minutes

As is clear from the experimental results shown in Fig. 1 and Table III, the coated granules of the present invention (coated with a coating dispersion containing citric acid in an amount of 3 parts by weight to 100 parts by weight of HPMCAS) showed much remarkably extended lag time in comparison with the coated granules of Comparative Example A (no citric acid was contained in the coating dispersion) and of Comparative Example B (citric acid was contained in an amount of 50 parts by weight to 100 parts by weight of HPMCAS). Thus, in the coated granules of Comparative Examples A and B, the medicament was almost dissolved out within a short period, but on the other hand, in the product of the present invention, the medicament was smoothly dissolved out after a lag time of several hours, from which it is considered that the preparation can release sufficiently after reaching to the large intestine.

The undersigned declares further that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the above-identified application or any patent issuing thereon.

This 14 day of December, 2005.

Tadashi Mukai

Tadashi Mukai